

PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Pharmaceutical Composition

I, EUSTACE CECIL BARTON-WRIGHT, a British subject of 10 Palliser Court, Palliser Road, London, W.14, England, (formerly of 113, Bishops Mansions, Bishops Park Road, London, S.W.6, England), do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a novel pharmaceutical composition of value in the treatment of osteoarthritis.

Experiments I have carried out indicate that osteoarthritis can be caused by metabolic disturbances. Whereas the quantities of α -ketoglutarate and of pyruvate excreted in the urine of humans have been used individually in the diagnosis of certain diseases, as far as I am aware no one has ever used the urinary α -ketoglutarate:pyruvate ratio in diagnosis. I have found that this ratio for "normals" (i.e., non-sufferers from rheumatoid arthritis or from osteoarthritis) generally lies between 0.3 and 1.2, the average being about 0.77. This ratio for sufferers from rheumatoid arthritis or for slight sufferers from both rheumatoid arthritis and osteoarthritis is commonly 1.2 to 1.7; for sufferers from severe osteoarthritis the ratio is commonly 1.7 to 4.0.

These and other results suggested to me that rheumatoid arthritis and osteoarthritis can be caused by partial failure of the Krebs cycle (i.e. the citric acid cycle). I have now discovered that administration of pantothenic acid and cysteine or cystine (or a physiologically acceptable salt of either) provides good relief to sufferers from osteoarthritis. Pantothenic acid, and 2-mercaptoethylamine, metabolically derived from cysteine or cystine, form part of co-

enzyme A, a vital reactant in the Krebs cycle. Although it has previously been suggested to use calcium d-pantothenate for the alleviation of arthritis I have found that greatly improved results are obtained in the treatment of osteoarthritis if a pantothenate and cysteine or cystine (or physiologically acceptable salts thereof) are administered conjointly to the patient.

According to the invention, therefore, I provide a pharmaceutical composition in which the active ingredients consist essentially of d-pantothenic acid or a physiologically acceptable salt thereof and cysteine or cystine (or a physiologically acceptable salt of either). The use of cysteine is preferred, but cystine can be used in its place, although it may be slower-acting.

Preferred salts of d-pantothenic acid are the sodium and particularly the calcium salt. Cysteine may be used in the composition as the hydrochloride, since the free acid itself is unstable and rapidly oxidises in air to cysteic acid. An advantageous composition is one comprising calcium d-pantothenate and cysteine hydrochloride; the calcium salt is not quite as basic as the sodium salt, for example, and is less likely to liberate cysteine itself from cysteine hydrochloride.

The compositions according to the invention may be adapted for oral administration, when they are preferably solid and are conveniently presented in the form of dosage units, e.g., tablets, capsules, or dragees. Suitable excipients include for example starch, lactose and/or calcium phosphate. Alternatively, the compositions according to the invention may be adapted for parenteral administration, and may thus be supplied in the form of ampoules or multi-dose flasks. The carrier may be a

sterile, parenterally acceptable liquid, e.g., pyrogen-free water or aqueous polyvinylpyrrolidone, or arachis oil. Such compositions, especially those comprising an aqueous carrier, are preferably prepared and sealed under nitrogen or other inert gas, to avoid oxidation of the cysteine, cystine or salt thereof. The compositions may also be presented in the form of dry ampoules, the liquid carrier (e.g., pyrogen-free water) to be added immediately before injection. Compositions adapted to be administered with an aqueous carrier may contain physiologically acceptable, inert compounds such as salts, adapted to adjust the pH or osmotic pressure of the compositions.

The compositions may further be presented as suppositories, the carrier being a suppository base, e.g. cocoa butter or a glyceride.

The pharmaceutical composition according to the invention preferably contains d-pantothenic acid or a physiologically acceptable salt thereof, for example the calcium salt, and the cysteine, cystine or physiologically acceptable salt thereof in substantially equimolar proportions. A preferred composition is presented in the form of dosage units, each containing about 25 mg. of calcium d-pantothenate and about 15 mg. of cysteine hydrochloride. The cysteine hydrochloride can be replaced partly or wholly by a substantially equal weight of cystine hydrochloride. A particularly suitable excipient is calcium phosphate, to give a tablet of approximately 100 mg., but other excipients, e.g., lactose, may also be used.

If desired, the compositions according to the invention may contain a substance which, in conjunction with d-pantothenic acid, is especially useful for the treatment of rheumatoid arthritis, e.g., queen bee substance ("royal jelly"), ethyl n-heptyloxyacetate, or 10-hydroxy- Δ^2 -decenoic acid or a physiologically acceptable salt thereof. Such a composition should have an enteric coating or be disposed within an enteric container, as described in British Patent Specification No. 1,033,843. The composition preferably contains 10-hydroxy- Δ^2 -decenoic acid in an amount 4 to 20% by weight of the weight of pantothenic acid calculated as calcium d-pantothenate. Thus a given dosage unit according to the invention may contain 20 to 30 mg. of calcium d-pantothenate and from 2.5 to 10 mg., preferably 5 mg., of 10-hydroxy- Δ^2 -decenoic acid. The dosage unit may if desired be in two parts, e.g., a tablet having an enteric core, or a double-ended capsule having one end enteric-coated or a composition as described in British Patent No. 1,033,843 comprising an enteric-coated portion and a composition comprising d-pantothenic acid or a

physiologically acceptable salt thereof and the cysteine or cystine or salt thereof in the non-enteric coated portion.

10-Hydroxy- Δ^2 -decenoic acid may be synthetic or obtained from natural sources, e.g., royal jelly; if this acid is obtained from natural sources, it should preferably be substantially free from natural co-occurring contaminants.

The following are examples of suitable tablets according to the invention:

Example 1

Composition of one tablet:—

Calcium d-pantothenate	25 mg.	80
Cysteine hydrochloride or cystine hydrochloride	15 mg.	
Calcium phosphate	60 mg.	

The ingredients are thoroughly mixed and compressed into tablets.

Example 2

Composition of one tablet:—

Calcium d-pantothenate	25 mg.	90
Cysteine hydrochloride	15 mg.	
10-Hydroxy- Δ^2 -decenoic acid	5 mg.	
Calcium phosphate.	55 mg.	

The ingredients are thoroughly mixed and filled into hard gelatine capsules. The filled capsules are enteric coated with cellulose acetate phthalate or keratin.

WHAT I CLAIM IS:—

1. A pharmaceutical composition in which the active ingredients consist essentially of d-pantothenic acid or a physiologically acceptable salt thereof and cysteine or cystine (or a physiologically acceptable salt of either).
2. A composition as claimed in claim 1 in which the salt of d-pantothenic acid is the sodium or calcium salt.
3. A composition as claimed in claim 1 in which the active ingredients consist essentially of calcium d-pantothenate and cysteine hydrochloride.
4. A composition as claimed in claim 1 in which the active ingredients consist essentially of calcium d-pantothenate and cysteine.
5. A composition as claimed in claim 4 containing substantially equimolar proportions of the calcium d-pantothenate and of cysteine.
6. A composition as claimed in any of the preceding claims comprising a pharmaceutical carrier or excipient.
7. A composition as claimed in any of the preceding claims in the form of dosage units.
8. A composition as claimed in claim 7 in the form of tablets, capsules, dragees, or suppositories, or contained in ampoules

or multi-dose flasks for parenteral administration.

9. A composition as claimed in claim 8 in the form of tablets, capsules, or dragees, and comprising starch, lactose, and/or calcium phosphate as excipient.

10. A composition as claimed in claim 8 contained in ampoules or multi-dose flasks and comprising pyrogen-free water, aqueous polyvinylpyrrolidone, or arachis oil as excipient.

11. A composition as claimed in claim 10 contained in ampoules sealed under an inert gas.

12. A composition for parenteral administration as claimed in claim 8 in the form of dry ampoules.

13. A composition as claimed in claim 12 containing physiologically acceptable inert compounds adapted to adjust the pH or the osmotic pressure of the injectable compositions prepared therefrom.

14. A composition as claimed in claim 1 in the form of dosage units containing about 25 mg. of calcium d-pantothenate and about 15 mg. of cysteine hydrochloride.

15. A modification of the composition as claimed in any of the preceding claims in which the active ingredients further include queen bee substance, ethyl n-heptyloxyacetate, or 10-hydroxy- Δ^2 -decenoic acid or a physiologically acceptable salt thereof.

16. A composition as claimed in claim

15 adapted for oral administration and having an enteric coating or disposed in an enteric container.

17. A composition as claimed in claim 15 or claim 16 containing 10-hydroxy- Δ^2 -decenoic acid in an amount of 4 to 20% by weight of the weight of the d-pantothenic acid calculated as calcium d-pantothenate.

18. A composition as claimed in any of claims 15 to 17 in dosage unit form and containing 20 to 30 mg. of calcium d-pantothenate and from 2.5 to 10 mg. of 10-hydroxy- Δ^2 -decenoic acid.

19. A composition as claimed in claim 18 containing about 5 mg. of 10-hydroxy- Δ^2 -decenoic acid.

20. A composition as claimed in claim 1 substantially as herein described.

21. A composition as claimed in claim 1 substantially as herein described with reference to Example 1.

22. A composition as claimed in claim 15 substantially as herein described with reference to Example 2.

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